American Journal of Medical Genetics 66:453–456 (1996)

Unusual Complex of Ventral Midline Anomalies: A Multiple Congenital Anomalies/Mental Retardation Syndrome

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We report on an infant boy with facial anomalies, hypoplasia of corpus callosum, cerebral atrophy, cleft of lower sternum, absence of palpable medial abdominal muscles, omphalocele, hypospadias, and other anomalies. This combination of congenital anomalies seems not to have been described before. A clear distinction from other syndromes and associations with midline defects seems possible, and thus a specific entity may be postulated. © 1996 Wiley-Liss, Inc.

KEY WORDS: omphalocele, cleft sternum, midline defect, MCA/MR syndrome

INTRODUCTION

Syndromes and associations involving ventral midline defects are of special interest to geneticists and embryologists. Opitz [1993] pointed out that midline formation during gastrulation is one of the most important functions in early blastogenesis. Disturbances during this developmental phase therefore lead to alterations of normal midline structures. Pathogenetically, the pentalogy of Cantrell (midline supraumbilical abdominal defect, defect of the lower sternum, cardiac anomalies, deficiency of the anterior diaphragm, and diaphragmatic pericardium) [Cantrell et al., 1958; Toyama, 1972; Zachariou et al., 1987; Carmi and Boughman, 1992], abdominal raphé syndrome (supraumbilical midline abdominal raphé, sternal defect, partial ectopia cordis, and cavernous hemangioma of the face) [Leiber, 1982; Igarashi et al., 1985; Pasic et al., 1993], and midline cervical cleft [Szenes, 1922; Godbersen et al., 1987] belong to this group. Regulation of midline formation also involves X-linked [Toriello and Higgins, 1985] and autosomal [Jespers et al., 1993; Bird et al., 1994] genes. We describe here an unusual combination of congenital midline anomalies and speculate on the pathogenesis.

Received for publication February 17, 1996; revision received May 17, 1996.

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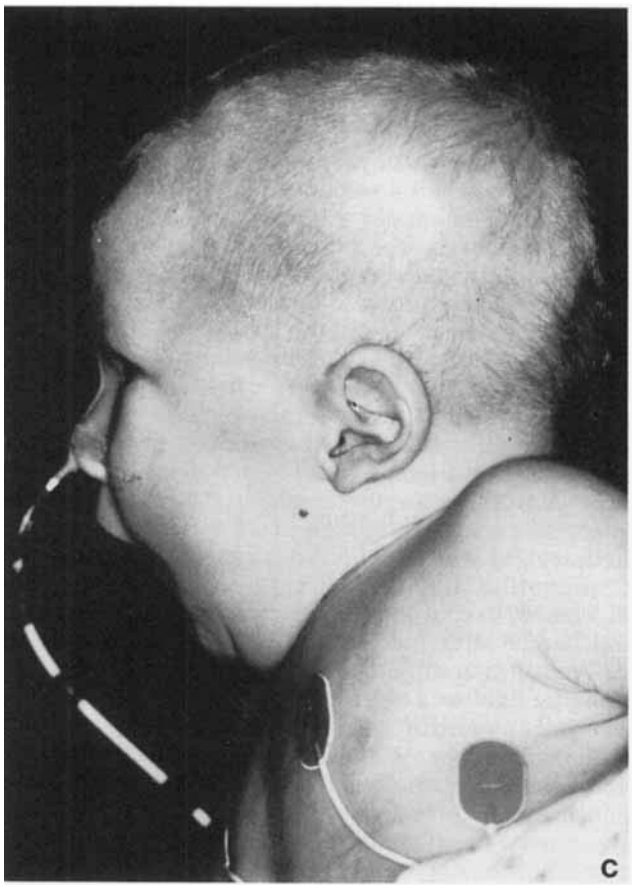
CLINICAL REPORT

P.V. was born to a 29-year-old mother and 32-year-old father. The boy is the second child of this healthy, nonconsanguineous couple; his older brother is normal. The pregnancy was complicated by polyhydramnios requiring nine amniocenteses, with weekly removal of 850–1,200 ml of amniotic fluid during the 25th–34th gestational weeks. The mother was not (pre)diabetic and there was no history of infections or drugs taken during the pregnancy. Weekly ultrasonography, from the 19th gestational week on, showed a prominent fetal abdomen without regular abdominal wall muscles; an omphalocele was suspected. There was no fetal urinary tract obstruction, ascites, or edema. The child was born by elective cesarean section at 36 weeks of gestation; birth weight was 3,300 g (90th centile), length 47 cm (25th centile), and occipitofrontal circumference (OFC) 36.5 cm (97th centile). Apgar scores were 3 after 1 min, and 7 and 8 after endotracheal intubation and mechanical ventilation after 5 and 10 min, respectively. The amniotic fluid was clear, and the placenta was macroscopically and histologically normal.

The infant appeared macrocephalic with short trunk, small thorax, plagiocephaly, blepharophimosis, downslanting palpebral fissures, apparent hypertelorism, hypoplastic nasal septum, tented upper lip, thin lips, micrognathia, apparently low-set ears, short neck, cavernous hemangioma below the left ear measuring 3 mm in diameter, webbing of the neck, and wide intermammillary distance (Fig. 1). A cleft of the lower sternum could be palpated. The belly was distended, with a lack of palpable medial abdominal muscles. The cord inserted in a 2 × 3 cm area, and there was a small omphalocele (Fig. 2). The penis was relatively small, with glandular hypospadias and descended testes. There was camptodactyly of the three middle fingers of both hands, with extended fifth fingers (Figs. 1d, 3). Active elevation of the tongue was virtually absent, and no rhythmic sucking and swallowing were seen on ultrasonography. Sensitivity of palate, supraglottis, and glottis was greatly reduced. Ophthalmological examinations showed a poorly pigmented periphery of the



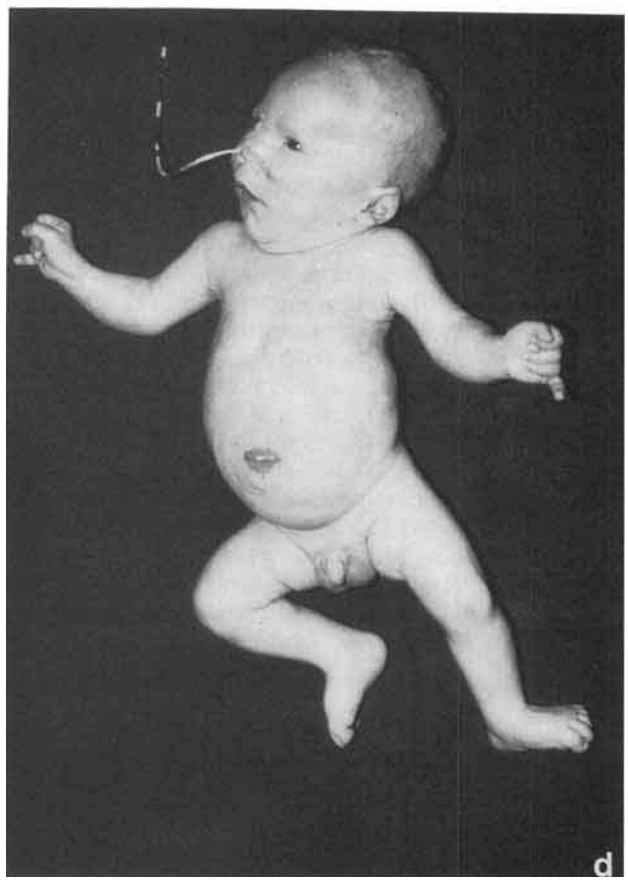


Fig. 1. Patient at age 2 days (**a**), and age 2 ½ months (**b–d**).

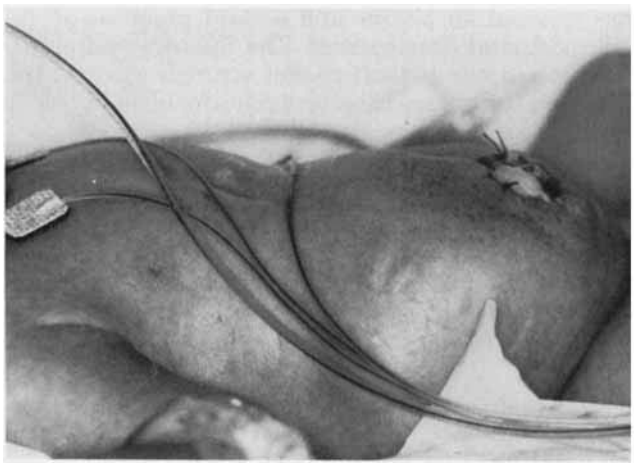


Fig. 2. Abdomen on second day of life. Note prune belly and cord insertion.

Fig. 3. Right hand. Note contractures of the three middle fingers.

fundus, but no microphthalmia. Echocardiography demonstrated a broad aneurysm of the ductus arteriosus (which resolved spontaneously) and a secundum-type atrial septal defect (ASD). On X-ray films a bell-shaped thorax was visible (Fig. 4). Pyeloureterography showed an enlarged right kidney but no signs of urinary tract obstruction. Cranial MRI disclosed brain atrophy with enlargement of the ventricles and of the external cerebrospinal fluid spaces (especially frontotemporal), and delayed myelinization and hypoplasia of the corpus callosum. Electroencephalography (EEG) at age 2 weeks and at 10 months, motor nerve conduction velocity and somatosensory-evoked potentials of the median nerve, and electromyogram (EMG) of the vastus lateralis muscle all were normal.

Testing for neonatal infections was negative. There was no lactic acidemia and results of metabolic investigations were normal, as were the G-banded chromosomes in amniocytes and peripheral lymphocytes, and dermatoglyphics.

The clinical course was characterized by a primary respiratory insufficiency which required mechanical ventilation up to day 31 of life and continuous positive airway pressure (CPAP) ventilatory support for a further 24 days. Feeding was by nasogastric tube, even after discharge from the hospital at 108 days.

Fig. 4. Radiograph of bell-shaped thorax.

Now at age 19 months, tube feeding is still necessary for fluids, but over the last 3 months the boy has learned to swallow mashed food. His motor development appears to be delayed, with sitting at age 16 months and standing and walking with support now. There is no speech yet, but according to the parents the boy seems to hear and see.

DISCUSSION

Our patient has a complex set of anomalies which raise causal and pathogenetic questions.

The infant's disproportionate birth weight-for-length may reflect lymphedema with minimal prenatal growth retardation. The other anomalies seem to represent a true multiple congenital anomalies/mental retardation (MCA/MR)-dysplasia syndrome including malformations, minor anomalies, and delayed psychomotor development associated with a primary central nervous system (CNS) defect.

The *malformations* include cleft lower sternum, omphalocele, hypospadias, aneurysm of ductus arteriosus, ASD, and hypoplasia of corpus callosum.

The *minor anomalies* include abnormal configuration of relatively small auricles, small and downslanting palpebral fissures, flat philtrum, hypoplastic nasal septum, and enlarged right kidney.

The 3-mm cavernous hemangioma below the left ear is a genuine *dysplasia*; its developmental fate will be of great interest.

The CNS "lesion" appears to dominate the picture and to have done so since before birth. It is characterized anatomically as an "atrophic" brain with enlargement of ventricles and the external cerebrospinal fluid spaces, and delayed myelinization and hypoplasia of the corpus callosum. Prenatally, this defect of CNS morphogenesis manifested itself with an apparent swallowing defect of the fetus with micrognathia and severe polyhydramnios, congenital movement disorder with plagiocephaly, micrognathia, camptodactyly, impaired function of a deformed, bell-shaped thorax, and neonatal respiratory

dysfunction requiring intubation, mechanical ventilation, and CPAP for the first 55 days of life. Failure to observe normal prenatal sucking and swallowing correlates with postnatal impairment of sensation of palate, glottis, and supraglottic area, and swallowing/feeding difficulties requiring tube feedings even after age 4 months. The fact that his fundi (at least the periphery) were "poorly" pigmented suggests early involvement of eyes, perhaps already at the time of primary CNS formation. Motor development is delayed, and the prognosis for hearing, vision, and cognitive development is guarded; results of electroretinographic and brain-stem auditory-evoked responses are pending.

The distended abdomen may represent an extreme diastasis recti abdominis or a developmental absence of medial abdominal wall muscles.

Thus, phenotype analysis suggests that this infant's MCA/MR syndrome 1) is dominated by a severe CNS anomaly/dysfunction; 2) arose during blastogenesis but continued into organogenesis and phenogenesis; and 3) may be regarded as a syndrome. It seems far more likely that this infant's condition represents pleiotropy rather than an association, since the latter, defined as multiple idiopathic anomalies of blastogenesis [Opitz, 1993], usually is *not* associated with multiple minor anomalies. Pleiotropy, i.e., the multiple manifestations of a single cause over several developmental periods, may represent the developmental effect of several categories of causes.

Aneuploidy, cryptic mosaicism, and uniparental disomy (UPD) are not automatically ruled out on the basis of an apparently normal amniocyte and postnatal lymphocyte analysis; and, in view of this infant's previously apparently undescribed syndrome, an analysis for mosaicism in fibroblasts and UPD are not unreasonable suggestions.

This does not seem to represent a known Mendelian mutation on the basis of extensive searches in OMIM, POSSUM, Medline, and the London Dysmorphology Database.

The infant's syndrome is atypical and his mother was not (pre)diabetic during her pregnancy with the boy; thus, it may be a fruitless effort to search for the mtDNA np 3243 LeutRNA A→G transversion that was described in an infant with VATER (vertebral defects, anal atresia, tracheoesophageal fistula with esophageal atresia, renal defects, and radial limb defects) association [Damian et al., 1996] and in an infant with multiple malformations of a mother with insulin-dependent diabetes due to this MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) mutation [Feigenbaum et al., 1996]. However, the 4 infants described by Cormier-Daire et al. [1996] with other congenital mitochondrial metabolic defects had malformations and multiple minor anomalies; thus, it may be possible that this infant has such an energy defect that, because of unfavorable heteroplasmy, has affected all phases and several processes of pre- and postnatal development. The findings and clinical outcome in our patient do not strongly suggest this; however, the results of tests of mitochondrial metabolic function are still pending.

ACKNOWLEDGMENTS

The authors are grateful to J.M. Opitz, M.D. (Helena, MT), for helpful discussion, to Dr. W. Grote (Kiel, Germany) for cytogenetic studies, and to Dr. V. Schulz (Kiel, Germany) for referring obstetric histories.

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